Official Title: **A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of INCB001158 in Combination With Chemotherapy, in Subjects With Advanced or Metastatic Solid Tumors**

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STATISTICAL ANALYSIS PLAN

INCB 01158-203

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of INCB001158 in Combination With Chemotherapy, in Subjects With Advanced or Metastatic Solid Tumors

IND Number:	[redacted]
EudraCT Number:	**2017-002904-29**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 4 dated 09 DEC 2020**
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SAP Author:	[redacted], PhD [redacted]
Date of Plan:	**08 MAR 2021**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
$AUC_{0-\tau}$	area under the steady-state plasma or serum concentration-time curve over 1 dose interval
BID	twice daily dosing
BOIN	Bayesian Optimal Interval
BOR	best overall response
BTC	biliary tract cancer
BUN	blood urea nitrogen
CI	confidence interval
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
CR	complete response
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EC	endometrial cancer
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FDA	Food and Drug Administration
GC	gastroesophageal cancer
IC_{90}	concentration that results in 90% inhibition
irAE	immune-related adverse event
[redacted]	[redacted]
IV	intravenously

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MSS	microsatellite stable
MTD	maximum tolerated dose
NE	not evaluable
OC	ovarian cancer
ORR	objective response rate
[redacted]	[redacted]
PAD	pharmacologically active dose
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response
PT	preferred term
QTc	corrected QT interval
QTcB	QT interval corrected using the Bazett method
QTcF	QT interval corrected using the Fridericia formula
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	recommended Phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time of occurrence of C_{max}
WHO	World Health Organization

1. INTRODUCTION

This is an open-label, nonrandomized, Phase 1/2 study to evaluate the safety, tolerability, and antitumor activity of INCB001158 in combination with 3 different chemotherapy regimens. Phase 1 consists of dose escalation using a BOIN design and will determine the RP2D of INCB001158 when given in combination with each chemotherapy regimen; efficacy will also be explored. Participants with advanced or metastatic solid tumors for whom treatment with one of the chemotherapy regimens is appropriate are enrolled in Phase 1.

Phase 2 evaluates ORRs using a Simon 2-stage design to determine whether the combinations have sufficient antitumor activity to warrant further testing in subsequent clinical studies and will further evaluate the safety and tolerability of the RP2D of INCB001158 when given in combination with chemotherapy. Participants with advanced or metastatic CRC, BTC, OC, GC, and EC are enrolled in the Phase 2 expansion cohorts.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 01158-203 Protocol. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee. The analyses of [redacted] PK [redacted] not described in this SAP.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 01158-203 Protocol Amendment 4 dated 09 DEC 2020 and CRFs approved 10 DEC 2020. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1: To assess the safety and tolerability, and determine the RP2D of INCB001158 in combination with chemotherapy.	Safety, tolerability, DLTs, and RP2D of INCB001158 in combination with chemotherapy, as assessed by AEs, clinical laboratory tests, physical examination results, and 12-lead ECG results.
Phase 2: To evaluate the efficacy of INCB001158 when given in combination with chemotherapy by assessing ORR per RECIST v1.1.	ORR, defined as the percentage of participants having a CR or PR, as determined by investigator assessment of radiographic disease assessments per RECIST v1.1.
Secondary	
Phase 2: To assess the safety, tolerability, and RP2D of INCB001158 in combination with chemotherapy	Safety and tolerability at RP2D of INCB001158 in combination with chemotherapy, as assessed by AEs, clinical laboratory tests, physical examination results, and 12-lead ECG results.
To evaluate the antitumor effect of INCB001158 in combination with chemotherapy	• ORR, defined as the percentage of participants having a CR or PR, as determined by investigator assessment of radiographic disease assessments per RECIST v1.1 (Phase 1 only). • DOR, defined as the time from the earliest date of CR or PR until earliest date of disease progression or death due to any cause, if occurring sooner than progression, as determined by investigator assessment of radiographic disease assessments per RECIST v1.1. • DCR, defined as the percentage of participants having a CR, PR, or SD for at least 8 weeks, as determined by investigator assessment of radiographic disease assessments per RECIST v 1.1. • PFS, defined as the time from the date of first dose of study drug until the earliest date of disease progression or death due to any cause, if occurring sooner than progression, as determined by investigator assessment of radiographic disease assessments per RECIST v1.1.
To determine the PK of INCB001158 in participants treated with INCB001158 in combination with chemotherapy.	PK of INCB001158 will be assessed by summarizing C_{max}, t_{max}, C_{min}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\tau}$.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. STUDY DESIGN

This is an open-label, nonrandomized, Phase 1/2 study to evaluate the safety, tolerability, and antitumor activity of INCB001158 in combination with 3 different chemotherapy regimens.

[redacted]

[redacted]

3.1. Phase 1 – Dose Escalation

In Phase 1, a BOIN design will be used to determine the RP2D of the combination of INCB001158 and chemotherapy in 21-day (for gemcitabine/cisplatin) or 28-day (for mFOLFOX6 or paclitaxel) treatment cycles in participants with advanced or metastatic solid tumors. The RP2D will then be further assessed in tumor expansion cohorts in Phase 2.

Dose escalation will begin with a starting dose (50 mg BID) of INCB001158 at least 2 dose levels below the maximum tolerated and tested dose from Study INCB 01158-101. The doses of INCB001158 to be evaluated and the scenarios for dose escalation and de-escalation are summarized in Table 2.

Table 2: INCB001158 Dose Levels and Cohorts

INCB001158 Dose Cohort	INCB001158 Dose Levels for Phase 1
-1	25 mg BID
1 (starting dose)	**50 mg BID**[a]
2	75 mg BID
3	100 mg BID
4	150 mg BID

[a] If INCB001158 50 mg BID is not tolerated within a treatment group, INCB001158 25 mg BID may be evaluated.

The INCB001158 dose will be escalated using an open-label BOIN design in each chemotherapy regimen, and a PAD or the MTD will be determined, or the maximum dose of INCB001158 (150 mg BID) will be reached. A PAD of INCB001158 is defined as a dose that achieves a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥ 1 μM that is equivalent to the IC_{90} for arginase 1. This definition may be modified based on emerging data from Study INCB 01158-101, the first-in-human study, upon agreement between the medical monitor and the study investigators. The MTD is the maximum tolerated or tested dose of INCB001158, such that fewer than 33% of the participants receiving the combination experience a DLT during the first 28 days on study drug. After the dose escalation is completed, one of the INCB001158 dose levels that is pharmacologically active and tolerable in combination with each chemotherapy regimen (ie, MTD or lower) will be the RP2D.

Dose interruptions and/or modifications may be implemented based on toxicity. Dose modifications should not be made during the DLT observation period without discussion with the medical monitor. Intraparticipant dose escalation is not permitted.

Dose escalation and de-escalation in Phase 1 will follow the BOIN design algorithm. Given the target DLT rate of 33% for the INCB001158 in combination with chemotherapy, the dose escalation and de-escalation rules are shown in Table 3. The BOIN design also includes an elimination rule. When ≥ 3 participants have been treated, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at a certain dose level, then this dose level and higher dose levels are assumed to be too toxic and will be eliminated. If the lowest dose level is eliminated, then the whole dose escalation will be terminated. Table 3 (in the bottom row) provides the elimination rules. Based on this algorithm, a minimum of 3 evaluable participants and a maximum of 9 evaluable participants will be enrolled at each tested dose level. The dose escalation will continue, based on the rules in Table 3, until at least 1 of the following occurs:

- Enrollment of additional participants in a dose cohort that already has 9 evaluable participants, or
- Dose escalation to a dose level that has already been eliminated, or
- Dose escalation above the maximum allowable dose level identified in Study INCB 01158-101.

At that point, the dose escalation will be stopped.

Table 3: Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate of 33% in Phase 1

Action	Number of Participants Treated at the Current Dose								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[a]**
Escalate if # of DLTs ≤	0	0	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	4	4
Elimination if # of DLTs ≥	N/A	N/A	3	3	4	4	5	5	6

[a] If 9 evaluable participants are enrolled in a dose cohort, and 3 of those participants experience a DLT, the medical monitor and the investigators will review the entirety of the data and decide whether to escalate the dose level, de-escalate the dose level, or stop at that dose level.

When applying the BOIN design, a maximum of 9 evaluable participants will be used at each dose level for initially identifying the MTD; however, the MTD of INCB001158 for one of the chemotherapy combinations may be a dose level below the other MTDs. After the PADs or MTDs are selected for each of the 3 combinations, the cohort may be expanded to 12 (and then to 15) in one of the chemotherapy combinations, and an MTD will be redetermined if all the following conditions are satisfied:

- If, and only if, a single one of the chemotherapy combinations has a lower MTD than the others.
- The Incyte medical monitor and the investigators review the entirety of the safety data and agree that the dose with the lower MTD needs to be re-challenged.
- The de-escalation and elimination boundaries are not crossed during the dose rechallenge and dose levels are retested. (Neither the de-escalation nor the elimination boundaries are touched.)

For expanding the cohorts, the decisions rules are presented in Table 4.

Table 4: Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate of 33% for Cohort Expansion in Phase 1

Action	Number of Participants Treated at the Current Dose					
	10	**11**	**12**	**13**	**14**	**15**
Escalate if # of DLTs ≤	2	2	3	3	3	3
De-escalate if # of DLTs ≥	4	5	5	6	6	6
Elimination if # of DLTs ≥	6	7	7	8	8	8

[redacted]

3.2. Phase 2 – Tumor Expansion Cohorts

To determine whether the combinations result in adequate ORRs to warrant further testing in subsequent clinical studies, a Simon 2-stage design will be used for each tumor expansion cohort to evaluate the ORR of the RP2D of INCB001158 determined in Phase 1 in combination with chemotherapy and to further evaluate the safety and tolerability of the combination. If, at the time of completion of enrollment in Stage 1, it is not known whether the target ORR to proceed to Stage 2 will be met, then enrollment will be paused until and unless the ORR to proceed has been met.

Enrollment in a specific expansion cohort will begin when the RP2D of INCB001158 for the corresponding treatment group in Phase 1 has been determined.

The expansion cohorts will be limited to the following advanced/metastatic or recurrent tumor types:

- Cohort A1: MSS-CRC (INCB001158 + mFOLFOX6)
- Cohort B1: BTC (INCB001158 + gemcitabine/cisplatin)
- Cohort B2: OC (INCB001158 + gemcitabine/cisplatin)
- Cohort C1: GC (INCB001158 + paclitaxel)
- Cohort C2: EC (INCB001158 + paclitaxel)
- Cohort C3: OC (INCB001158 + paclitaxel)

Continuous evaluation of toxicity events will be performed in the expansion cohorts. If the cumulative incidence of ≥ Grade 3 INCB001158-related AEs or ≥ Grade 3 chemotherapy-related AEs is > 40% after 10 participants are enrolled in a specific expansion cohort within Phase 2, then further enrollment in that cohort will be interrupted until the sponsor and investigators determine the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

In each cohort, a Simon 2-stage design (see Table 5) will be used to assess the antitumor activity of the INCB001158 + chemotherapy combination to determine whether the combination results in sufficient antitumor activity to warrant further testing in subsequent clinical studies. See Sections 1.1 and 1.2 of the Protocol for background and target ORRs rational for each cohort.

Table 5: Phase 2: Simon 2-Stage Design

Cohort (Tumor Type)	Background ORR	Target ORR	Alpha	Power (%)	N for Stage 1	ORR to Proceed	N for Stage 2	ORR for Positive Cohort
A1 (MSS-CRC)	10%	30%	0.1	80	7	≥ 1/7	11	≥ 4/18
B1 (BTC)	20%	40%	0.1	80	12	≥ 3/12	13	≥ 8/25
B2 (OC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C1 (GC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C2 (EC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C3 (OC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23

3.3. Control of Type I Error

For the primary efficacy endpoints, the 1-sided Type I error will be controlled at 0.1 for each individual cohort expansion. Note that this level of significance does not account for the multiple expansion cohorts. For other endpoints, CIs will be reported at a 95% confidence level.

3.4. Sample Size Considerations

3.4.1. Sample Size for Phase 1

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 when given in combination with chemotherapy in participants with advanced or metastatic solid tumors. The details of the dose escalation, de-escalation, and elimination rules according to the BOIN design are provided in Section 3.1.

3.4.2. Sample Size for Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of INCB001158 in combination with chemotherapy. A Simon 2-stage design will be run for each tumor type within a given expansion cohort.

The sample size for each tumor type within a given expansion cohort will be guided by the Simon 2-stage design. The planned Simon 2-stage designs are summarized in Table 5. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular tumor type within the given cohort at the end of Stage 1 if there is insufficient response observed, while enrolling enough participants to predict possible target responses worthy of cohort expansion and potentially further evaluation in future studies. The individual Simon 2-stage designs run for each tumor type within each cohort will have design parameters that are determined by historical response rates.

In order to determine whether the target response rate (p_1%) is likely, an initial number of evaluable participants (n_1 participants) will be treated at the RP2D of INCB001158 in combination with each chemotherapy (Stage 1). If there are r_1 or fewer responses in the expansion cohort, then it will be concluded that the true response rate is unlikely to be ≥ the

target rate, and no more participants will be enrolled in that tumor type for that cohort in Stage 2. In the cohorts in which > r_1 responses are observed among the Stage 1 participants, n_2 additional evaluable participants will be treated in Stage 2 to estimate the response rate. At the end of Stage 2, if ≤ r participants have responded among the n evaluable participants, then the drug will be declared nonpromising for that cohort. The detailed calculations for each tumor type–specific cohort are based on a 1-sided Type I error of 0.1 and power of 80%.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study treatment (INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel) is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of −1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose, and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose, and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

Partial disease diagnosis date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

Missing or partial date of last dose will be handled as follows:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the first day of the month or the date that the participant discontinued treatment.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial death date will be imputed as follows:

- If mmyyyy for the last contact date = mmyyyy for the death date, then the death date will be set to the day after the last contact date.
- If mmyyyy for the last contact date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel is administered. If mFOLFOX6, gemcitabine/cisplatin, or paclitaxel is discontinued, the cycle definition of INCB001158 can be maintained depending on the treatment group assigned (28 days for mFOLFOX6 and paclitaxel and 21 days for gemcitabine/cisplatin).

- **INCB001158:** In Phase 1 dose escalation, INCB001158 will be administrated PO BID with the dose corresponding to cohort assignment. In Phase 2 expansion cohorts, INCB001158 will be administrated PO BID at the RP2D determined in the dose escalation as long as the participant is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal.
- **mFOLFOX6**
  - Oxaliplatin 85 mg/m^2 IV on Days 1 and 15 of a 28-day cycle.
  - Leucovorin 400 mg/m^2 IV on Days 1 and 15 of a 28-day cycle.
  - 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Days 1 and 15 of a 28-day cycle.

- **Gemcitabine and Cisplatin:** Will be administered on Days 1 and 8 of a 21-day cycle. For Phase 1 dose escalation, participants with advanced or metastatic disease will receive gemcitabine 1000 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 30 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle. For Phase 2 tumor expansion cohorts, participants will receive the gemcitabine/cisplatin regimen that is the standard dose and schedule used for the corresponding tumor type:
  - Cohort B1 (BTC): Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle and cisplatin 25 mg/m^2 IV infusion on Days 1 and 8 of each 21-day cycle.
  - Cohort B2 (OC): Gemcitabine 750 mg/m^2 IV infusion and cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle.
- **Paclitaxel:** Will be administrated weekly at 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle.

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Age

Participant age will be calculated as the integer part of the number of years from date of birth to the date of signing the ICF, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1) / 365.25.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel and is ongoing or ends during the course of study drug.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

In Phase 1, a BOIN design will be used to determine the RP2D of the combination of INCB001158 and chemotherapy in 21-day (for gemcitabine/cisplatin) or 28-day (for mFOLFOX6 or paclitaxel) treatment cycles in participants with advanced or metastatic solid tumors. The RP2D will then be further assessed in tumor expansion cohorts in Phase 2.

Participants with advanced or metastatic solid tumors will be assigned to 1 of the treatment groups summarized in Table 6 based on the chemotherapy regimen most appropriate for the participant's tumor type.

Table 6: Treatment Groups for Participants Enrolled in Phase 1 Dose Escalation

Treatment Group A	**INCB001158**	**mFOLFOX6**
	25-150 mg PO BID continuous daily dosing	• Oxaliplatin 85 mg/m^2 IV on Days 1 and 15 of a 28-day cycle • Leucovorin 400 mg/m^2 IV on Days 1 and 15 of a 28-day cycle • 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Days 1 and 15 of a 28-day cycle
Treatment Group B	**INCB001158**	**Gemcitabine and Cisplatin**
	25-150 mg PO BID continuous daily dosing	• Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle • Cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Treatment Group C	**INCB001158**	**Paclitaxel**
	25-150 mg PO BID continuous daily dosing	Paclitaxel 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle

In Phase 2, the expansion cohorts will be limited to the advanced/metastatic or recurrent tumor types summarized in Section 3.2. Participants will be assigned to the expansion cohorts summarized in Table 7.

Table 7: Expansion Cohorts for Participants Enrolled in Phase 2 Tumor Expansion

Expansion Cohort A1	**INCB001158**	**mFOLFOX6**
	PO BID continuous daily dosing	• Oxaliplatin 85 mg/m^2 IV on Days 1 and 15 of a 28-day cycle • Leucovorin 400 mg/m^2 IV on Days 1 and 15 of a 28-day cycle • 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Days 1 and 15 of a 28-day cycle
Expansion Cohort B1	**INCB001158**	**Gemcitabine and Cisplatin**
	PO BID continuous daily dosing	• Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle • Cisplatin 25 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Expansion Cohort B2	**INCB001158**	**Gemcitabine and Cisplatin**
	PO BID continuous daily dosing	• Gemcitabine 750 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle • Cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Expansion Cohorts C1, C2, and C3	**INCB001158**	**Paclitaxel**
	PO BID continuous daily dosing	Paclitaxel 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle

5.3. Analysis Populations

For all populations, for safety (exposure, AE, laboratory, ECG, and vital sign) analysis, Phase 1 and Phase 2 FAS populations will be combined, and table summaries will be provided by treatment group and dose level; for disposition, baseline and demographic characteristics, prior and concomitant medication, medical history, and efficacy analysis, table summaries will be provided by treatment group and dose level for Phase 1 and by treatment group and expansion cohort (tumor type) for Phase 2.

5.3.1. Full Analysis Set

The FAS population includes all participants enrolled in the study who received at least 1 dose of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel. This population will be used in the analyses of demographic, baseline, safety, study treatment administration, PFS, [redacted] data.

5.3.1.1. mFOLFOX6 FAS Population

The mFOLFOX6 FAS population includes all participants in the FAS population who received at least 1 dose of any component of mFOLFOX6 (oxaliplatin, leucovorin, or 5-fluorouracil).

5.3.1.2. Gemcitabine/Cisplatin FAS Population

The gemcitabine/cisplatin FAS population includes all participants in the FAS population who received at least 1 dose of gemcitabine or cisplatin.

5.3.1.3. Paclitaxel FAS Population

The paclitaxel FAS population includes all participants in the FAS population who received at least 1 dose of paclitaxel.

5.3.2. Response Evaluable Population

The response evaluable population includes all participants who received at least 1 dose of study treatment (INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel), completed a baseline scan, and met at least 1 of the following criteria:

- The participant had ≥ 1 postbaseline scan.
- The participant was on the study for a minimum of 63 days (8 weeks + 1 week window) days of follow-up.
- The participant discontinued from study treatment.

5.3.3. DLT Evaluable Population in Phase 1

The DLT evaluable population includes participants enrolled in Phase 1 treated with the assigned dose level of INCB001158 and who have received at least 32 of the 42 doses to be given in a 21-day cycle regimen, or at least 42 of the 56 doses prescribed for a 28-day cycle regimens (both representing ≥ 75% of the dose planned), or participants who have had a DLT. This population will be considered evaluable for determining the tolerability of the given dose.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

A list of data displays will be provided in Appendix A, and the sample data displays will be provided in a separate document.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographic Characteristics

The following demographic characteristics will be summarized for all participants in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type: age, sex, race, ethnicity, weight, height, and ECOG performance status.

6.1.2. Baseline Disease Characteristics and Disease History

Primary tumor histology, time from initial diagnosis in months, stage at initial diagnosis, current stage of disease, current site of disease, tumor markers, and ECOG performance status will be summarized for all participants in the Phase 1 FAS population by treatment group and dose level, and Phase 2 FAS population by treatment group and tumor type. Tumor type–specific baseline characteristics and disease history will be summarized for the Phase 2 FAS population by treatment group and tumor type and will be provided in the listing for the Phase 1 FAS population by treatment group and dose level.

6.1.3. Prior Therapy

Prior systemic cancer therapy regimens will be summarized by total number and by number of prior systemic cancer therapies taken for both advanced and metastatic disease for all participants in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. Regimen name, component drugs, start and stop date, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

The number (%) of participants who received prior radiation will be summarized in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. Radiotherapy type, body site, start and stop date, total dose, and best response will be listed.

The number (%) of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. Date and description of the surgery/procedure will be listed.

6.1.4. Medical History

Medical history will be summarized in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. This summation will include the number and percentage of participants with significant medical history for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participants

The number and percentage of participants who were enrolled, screened, screen failed, treated, completed the study, discontinued study treatment with a primary reason for discontinuation, and withdrew from the study with a primary reason for withdrawal will be summarized in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. The number of participants enrolled by country and site will also be provided by treatment group.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be presented in a table and in the participant data listings.

6.4. Exposure

6.4.1. Exposure for INCB001158

For participants in the Phase 1 and Phase 2 combined FAS population, exposure to INCB001158 will be summarized descriptively as the following:

- **Total actual dose (mg):** Total actual dose taken of INCB001158.
- **Duration of treatment (day):** Date of last dose of INCB001158 – date of first dose of INCB001158+1.

- **Average daily dose (mg):** Total actual dose taken on INCB001158 (mg) divided by the duration of INCB001158 with non-zero dosing (days).

6.4.2. Exposure for mFOLFOX6

For participants in the Phase 1 and Phase 2 mFOLFOX6 FAS populations, exposure to mFOLFOX6 will be summarized descriptively by dose level and treatment group as follows.

6.4.2.1. Exposure for Oxaliplatin

- **Number of Infusions:** Number of administered, non-zero infusions of oxaliplatin recorded on the Oxaliplatin Dosing eCRF.
- **Average Dose (mg/m^2):** Sum of the doses of oxaliplatin recorded (mg/m^2) on the Oxaliplatin Dosing eCRF divided by the number of infusions of oxaliplatin.
- **Dose Administered per Cycle (mg/m^2):** The actual dose of oxaliplatin administered (mg/m^2) per cycle.

6.4.2.2. Exposure for Leucovorin

- **Number of Infusions:** Number of administered, non-zero infusions of leucovorin recorded on the Leucovorin Dosing eCRF.
- **Average Dose (mg/m^2):** Sum of the doses of leucovorin recorded (mg/m^2) on the Leucovorin Dosing eCRF divided by the number of infusions of leucovorin.
- **Dose Administered per Cycle (mg/m^2):** The actual dose of leucovorin administered (mg^2) per cycle.

6.4.2.3. Exposure for 5-Fluorouracil

- **Number of Infusions:** Number of administered, non-zero infusions of 5-fluorouracil recorded on the 5-fluorouracil Dosing eCRF.
- **Average Dose (mg/m^2):** Sum of the doses of 5-fluorouracil recorded (mg/m^2) on the 5-Fluorouracil Dosing eCRF divided by the number of infusions of 5-fluorouracil.
- **Dose Administered per Cycle (mg/m^2):** The actual dose of 5-fluorouracil administered (mg/m^2) per cycle.

6.4.3. Exposure for Gemcitabine/Cisplatin

For participants in the Phase 1 and Phase 2 gemcitabine/cisplatin FAS populations, exposure to gemcitabine/cisplatin will be summarized descriptively by dose level and treatment group as follows.

6.4.3.1. Exposure for Gemcitabine

- **Number of Infusions:** Number of administered, non-zero infusions of gemcitabine recorded on the Gemcitabine Dosing eCRF.
- **Average Dose (mg/m^2):** Sum of the doses of gemcitabine recorded on the Gemcitabine Dosing eCRF divided by the number of infusions of gemcitabine.
- **Dose Administered per Cycle (mg/m^2):** The actual dose of gemcitabine administered (mg/m^2) per cycle.

6.4.3.2. Exposure for Cisplatin

- **Number of Infusions:** Number of administered, non-zero infusions of cisplatin recorded on the Gemcitabine/Cisplatin Dosing eCRF.
- **Average Dose (mg/m^2):** Sum of the doses of cisplatin recorded on the Cisplatin Dosing eCRF divided by the number of infusions of cisplatin.
- **Dose Administered per Cycle (mg/m^2):** The actual dose of cisplatin administered (mg/m^2) per cycle.

6.4.4. Exposure for Paclitaxel

For participants in the Phase 1 and Phase 2 paclitaxel FAS populations, exposure to paclitaxel will be summarized descriptively by dose level and treatment group as the following:

- **Number of Infusions:** Number of administered, non-zero infusions of paclitaxel recorded on the Paclitaxel Dosing eCRF.
- **Average Dose (mg/m^2):** Sum of the doses of paclitaxel recorded (mg/m^2) on the Paclitaxel Dosing eCRF divided by the number of infusions of paclitaxel.
- **Dose Administered per Cycle (mg/m^2):** The actual dose of paclitaxel administered (mg/m^2) per cycle.

6.5. Study Drug Compliance

For participants in the FAS, overall compliance (%) for INCB001158 will be calculated for all participants as

Overall compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator, accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the drug accountability CRF. If there is dispensed drug that has not been returned yet, the actual dose taken starting from the dispense date of the unreturned drug will be imputed by the dose taken as reported on the dosing CRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term in the Phase 1 FAS population by treatment group and dose level and the Phase 2 FAS population by treatment group and tumor type. Results will be summarized as number and percentage of participants with prior and concomitant medications by PT and WHO drug class.

7. EFFICACY

Appendix A provides a list of data displays.

7.1. General Considerations

The primary efficacy endpoint for this study is ORR by investigator assessment based on RECIST v1.1 assessed in the Phase 2 response evaluable population. Secondary efficacy endpoints of this study include ORR (Phase 1), DOR, DCR, and PFS by investigator assessment based on RECIST v1.1. [redacted]

7.2. Efficacy Hypotheses

Each Simon 2-stage design will test the null hypothesis that the true ORR is less than or equal to the clinically insignificant response rate p_0% against the alternative hypothesis that the true ORR is equal to the target rate of p_1%. For each Simon 2-stage design, the value for p_0 is determined by a historical response rate. The same values for p_0 and p_1 will be used for alternative dosing sequences in the same tumor type and treatment combination.

7.3. Analysis of the Efficacy Parameters

7.3.1. Response Criteria

Overall disease status will be categorized using RECIST v1.1. Participants will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiological assessment based on changes in target lesions, nontarget lesions, and appearance of new lesions.

7.3.2. Objective Response Rate and Best Overall Response

7.3.2.1. Confirmed ORR and Confirmed BOR by RECIST v1.1

Per RECIST v1.1, in nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses are not the result of measurement error. Therefore, a participant is defined as a confirmed objective responder if the participant has an overall response of CR or PR at any postbaseline visit that is confirmed at a subsequent timepoint at least 4 weeks later, or at the next scheduled scan (ie, 8 weeks later), whichever is clinically indicated, before the first occurrence of PD. Confirmed objective responders will be assessed based on RECIST v1.1.

Confirmed ORR is defined as the proportion of participants with confirmed objective responses of CR or PR. Confirmed ORR will be estimated with 95% CIs. Confidence intervals will be based on the method for Simon 2-stage CIs of response rates outlined in Koyama and Chen (2008).

Confirmed ORR will be summarized by treatment group and tumor type as primary endpoint for the Phase 2 response evaluable population.

In general, confirmed BOR is the best response recorded postbaseline prior to and including the first PD, before any new anticancer therapies, in the order of CR, PR, SD, PD and NE, in which CR and PR must be confirmed at a subsequent timepoint at least 4 weeks after the CR or PR is observed. Responses of CR, PR, or SD after the first assessment of PD will not be considered. In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 49 (= 56-7) days. Participants that fail to meet this criterion will have confirmed best overall response of PD, if the next available assessment indicates PD, or NE, if there is no additional assessment available.

Under RECIST v1.1, if radiologic imaging shows CR or PR, a tumor assessment should be repeated at a minimum of 4 weeks to confirm the response in order to claim the CR or PR as the confirmed BOR. If there is no second CR or PR tumor assessment, the CR or PR will be unconfirmed. Table 8 lists the scenarios of responses that can occur after an unconfirmed CR or PR and provides a rule for determining the confirmed BOR in each scenario.

For determination of confirmed BOR, confirmatory scans with a response of NE will be subsequently followed by another scan at a minimum of 4 weeks. For example, in the case of PR at the first timepoint followed by NE at a subsequent timepoint, if a third scan shows a PR then the confirmed BOR will be PR. There will be no third confirmatory scans performed for a loss of response. For example, if a response of PR at the first timepoint is followed by a response of SD or PD at a subsequent timepoint, the confirmed BOR will be determined using the rules in Table 8.

Table 8: Derivation of Confirmed Best Overall Response

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Confirmed Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD[a],provided minimum criteria for SD duration are met; otherwise, PD
CR	PD	SD[a], provided minimum criteria for SD duration are met; otherwise, PD
CR	NE	SD[a], provided minimum criteria for SD duration are met; otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration are met; otherwise, PD
PR	NE	SD[a], provided minimum criteria for SD duration are met; otherwise NE
NE	NE	NE

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Confirmed BOR would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had a PR, not a CR, at the first timepoint. Under these circumstances, the original CR should be changed to a PR, and the confirmed BOR is PR.

For participants with measurable disease at baseline, the RECIST v1.1 assessment criteria presented in Table 9 can be used to determine the overall disease status at a given timepoint based on the target lesion, nontarget lesion, and new lesion assessment.

Table 9: RECIST v1.1 Evaluation Criteria for Overall Response: Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.3.3. Duration of Response

For objective responders, the DOR is the time from the first overall response contributing to an objective response to the earlier of the participant's death or first overall response of PD as assessed by RECIST v1.1 occurring after the first overall response contributing to the objective response. Partial death dates will be handled using the rules described in Section 4.1.4. Censoring of DOR will follow the same algorithm as the censoring of PFS.

Kaplan-Meier curves for DOR will be presented by treatment group and dose level for the Phase 1 response evaluable population and by treatment group and tumor type for the Phase 2 response evaluable population. The Kaplan-Meier estimate of median DOR will be presented with its 95% CI. The 95% CI will be calculated using Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982).

7.3.4. Disease Control Rate

Disease control rate, defined as the proportion of participants who have disease control (CR + PR + SD for at least 8 weeks), as per RECIST v1.1 will be summarized. For the determination of DCR, responses of CR and PR do not need to be confirmed at a subsequent timepoint. In the case of SD, measurements must meet the SD criteria at least after the date of first dose at a minimum of 49 (= 56-7) days. Participants who fail to meet this criterion will have confirmed BOR of PD if the next available assessment indicated PD or NE if there is no additional assessment available. Disease control rate will be estimated with 95% CIs. Confidence intervals will be calculated based on the exact method for binomial distributions.

7.3.5. Largest Percent Reduction in Sum of Diameters of Target Lesions

For each participant in the response evaluable population with target lesions at baseline, target lesion sizes will be measured by sum of diameters. The best percentage change from baseline, defined as the largest decrease (or the smallest increase if there is no decrease) in target lesion size for each participant, will be summarized descriptively, and a waterfall plot of the best percentage change will be generated.

Per RECIST v1.1, target lesions considered "too small to measure" will be assigned a default value of 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that postbaseline timepoint.

7.3.6. Percentage Change in Sum of Diameters of Target Lesions Over Time

For each participant in the response evaluable population with target lesions at baseline, target lesion sizes will be measured by sum of diameters. The percentage change in sum of diameter of target lesions over time will be listed, and a spider plot will be generated.

7.3.7. Progression-Free Survival

Progression-free survival is defined as the length of time between the date of first dose of study drug and the earlier of death or PD as assessed by RECIST v1.1. Date of death will be

determined using the Death Report, the Survival Follow-Up, and the Subject Status eCRFs, and analyses will be summarized for the FAS population.

Censoring for PFS will follow the algorithm outlined in Table 10, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2015, FDA 2018).

Kaplan-Meier curves for PFS will be presented by cohort-specific tumor type. The Kaplan-Meier estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982).

Table 10: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of Day 1
No valid postbaseline response assessments	Censored	Date of Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing).
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after more than 1 missed assessment	Censored	Date of last valid radiologic assessment (not NE and not missing) before death

[redacted]

8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays.

8.1. General Considerations

Phase 1 and Phase 2 FAS populations will be combined for safety analysis, and table summaries will be provided by treatment group and dose level. Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

Unless otherwise stated, table summaries will be limited to TEAEs.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. For the participants in the FAS population, analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA v20.1 PT and SOC. Severity of AEs will be graded using the National Cancer Institute CTCAE. The CTCAE v4.03 is used for this study. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel will be considered to be treatment-related AEs and will be summarized. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, SAEs will also be tabulated.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v4.03 criteria, it will be rated on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death related to AE. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be collected as an AE until the event resolves. Only the worst grade will be reported in AE summaries. Also, the Grade 3 or higher AEs will be summarized.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

8.2.2. Dose-Limiting Toxicities

The number of participants in the DLT evaluable population with DLTs and the type of DLT will be listed by dose level and treatment group. An AE for a participant will be identified as a DLT if the event is recorded as a Protocol-defined DLT on the Adverse Event eCRF.

8.2.3. Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and any other observed autoimmune phenomenon.

An overall summary of irAEs by treatment group and dose level for the Phase 1 and Phase 2 combined FAS population as applicable will include the following:

- Number (%) of participants reporting any irAEs
- Number (%) of participants reporting any Grade 3 or higher irAEs
- Number (%) of participants reporting any irAEs related to INCB001158
- Number (%) of participants who had fatal irAEs
- Number (%) of participants who had irAEs leading to temporary interruption of INCB001158
- Number (%) of participants who had irAEs leading to permanent discontinuation of INCB001158
- Number (%) of participants who had irAEs leading to INCB001158 dose reductions

8.2.4. Adverse Event Summaries

An overall summary of AEs by treatment group and dose level for the Phase 1 and Phase 2 combined FAS population as applicable will include the following:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any SAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any TEAEs related to INCB001158
- Number (%) of participants reporting any TEAEs related to chemotherapy
- Number (%) of participants reporting any TEAEs related to INCB001158 and/or chemotherapy
- Number (%) of participants reporting any Grade 3 or higher TEAEs related to INCB001158
- Number (%) of participants reporting any SAEs related to INCB001158 and/or chemotherapy
- Number (%) of participants reporting any Grade 3 or higher TEAEs related to INCB001158 and/or chemotherapy

- Number (%) of participants who had TEAEs leading to temporary interruption of INCB001158
- Number (%) of participants who had TEAEs leading to permanent discontinuation of INCB001158
- Number (%) of participants who had TEAEs leading to INCB001158 dose reductions
- Number (%) of participants who had fatal TEAEs
- Number (%) of participants who had TEAEs leading to study withdrawal
- Number (%) of participants who had irAEs

The following summaries will be produced by MedDRA term for the Phase 1 and Phase 2 combined FAS population:

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or higher TEAEs by PT in decreasing order of frequency
- Summary of treatment-emergent SAEs by PT in descending order of frequency
- Summary of INCB001158 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of mFOLFOX6 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of gemcitabine/cisplatin treatment-related TEAEs by PT in decreasing order of frequency
- Summary of paclitaxel treatment-related TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or higher INCB001158 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to INCB001158 dose reduction by PT in decreasing order of frequency
- Summary of TEAEs leading to INCB001158 dose interruption by PT in decreasing order of frequency
- Summary of TEAEs leading to discontinuation of INCB001158 by PT in decreasing order of frequency
- Summary of immune-related TEAEs by PT in decreasing order of frequency

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. The baseline value will be determined using the nonmissing values collected before the first dose using the priority defined in Table 11. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Table 11: Identification of Baseline Record

Priority	Laboratory Visit	Central or Local Laboratory
1	Scheduled	Central
2	Scheduled	Local
3	Unscheduled	Central
4	Unscheduled	Local

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v4.03.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple nonmissing laboratory values for a participant's particular test within a visit window, the convention described in Table 12 will be used to determine the record used for by-visit tabulations and summaries. If a tie still exists, the laboratory value with the smallest laboratory sequence number will be used.

Table 12: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Central or Local Laboratory	Proximity to Visit Window	Tiebreaker
1	Scheduled	Central	In-window	Use smallest laboratory sequence number
2	Scheduled	Local	In-window	
3	Unscheduled	Central	In-window	
4	Unscheduled	Local	In-window	
5	Scheduled	Central	Out-of-window	
6	Scheduled	Local	Out-of-window	

For coagulation and urinalysis laboratory values, listings will be provided.

Numeric chemistry and hematology laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v4.03. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum severity.

In cases where differentials of hematology parameters are obtained without corresponding absolute count data, efforts will be made to investigate if the conversion to an absolute value will lead to additional abnormalities. This will be discussed with the clinical team regarding appropriate documentation and action.

8.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including systolic blood pressure and diastolic blood pressure, will be summarized descriptively. Listings will be provided for all vital sign parameters.

Normal ranges for vital sign values are defined in Table 13. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group.

Table 13: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24 breaths/min	< 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including heart rate, PR, QRS, QT, and QTc (or QTcF, QTcB) intervals will be obtained for each participant at the screening, end of treatment, and safety follow-up visits during the study. Baseline will be determined as the average of all nonmissing values before the first administration of INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel.

Normal ranges for ECG values are defined in Table 14. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Outliers of QT and QTcF values, defined as absolute values > 450 milliseconds, > 500 milliseconds, or change from baseline > 30 milliseconds, will be summarized.

Table 14: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
QTc, QTcF, QTcB	> 480 ms	< 295 ms
RR	> 1330 ms	< 600 ms

RR = 60,000 ms/heart rate.

9. INTERIM ANALYSES

9.1. Overview of Interim Analyses

9.1.1. Interim Analyses for the BOIN Design

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 in combination with each chemotherapy regimen. For the design parameters, let ϕ denote the target DLT rate, $\phi_1$denote the highest toxicity probability below the MTD so that dose escalation is required, and ϕ_2 denote the lowest toxicity probability deemed overly toxic so that dose de-escalation is required. We assume that $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$. Also, to avoid assigning too many participants to an overly toxic dose, we use the dose elimination rule when implementing the BOIN design. If $p_r(p_j > \phi|m_j,n_j) > 0.95$ and $n_j \geq 3$, then dose levels j and higher are eliminated from the study, and the study is terminated if the first dose level is eliminated, where p_j represents the toxicity rate, ϕ represents the target DLT rate, n_j represents the total participants who have been treated, and m_j represents the participants who have experienced toxicity at dose level j. Table 3 (in the bottom row) provides the elimination boundaries for the target DLT rate of 33%, respectively. For example, for the target DLT rate 33%, when the number of participants treated at the current dose $n_j = 4$, we will eliminate that dose and higher doses if 3 or more participants experience toxicity.

Based on the algorithm of the BOIN design, a minimum of 3 evaluable participants will be enrolled in each dose level with a maximum of 9 evaluable participants in each dose level.

9.1.2. Interim Analyses for the Simon 2-Stage Design

In Phase 2, there will be a planned interim analysis for futility in each of the 6 expansion cohorts. The Simon 2-stage design will be applied for each expansion cohort independently. During Stage 1, n_1 evaluable participants treated at the recommended dose and schedule will be enrolled (see Table 5), and if $r_1$or fewer responses are observed, then the cohort will be discontinued. The Simon 2-stage designs for each tumor type have design parameters determined by historical response rates and will have different sample sizes and different futility rules, depending on the historical response rate. Based on this early termination rule, the probabilities of early termination under the assumption of treatment interruption response rates (H_0) and desired response rates (H_A) are summarized in Table 15.

Table 15: Probability of Early Termination for Simon 2-Stage Design

Cohort (Tumor Type)	p_0	p_1	Probability of Early Termination	
			Under H_0	Under H_A
A1 (MSS-CRC)	15%	35%	0.5995	0.1211
B1 (BTC)	20%	40%	0.5583	0.0834
B2 (OC)	15%	35%	0.5995	0.1211
C1 (GC)	15%	35%	0.5995	0.1211
C2 (EC)	15%	35%	0.5995	0.1211
C3 (OC)	15%	35%	0.5995	0.1211

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 16.

Table 16: Statistical Analysis Plan Versions

SAP Version	Date
Original	26 JUL 2018
Amendment 1	08 MAR 2021

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

10.2.1. Original to Amendment 1

- [redacted]
- Section 5.3 was revised to change the general approach to display summary tables: for safety (exposure, AE, laboratory, ECG, and vital sign) analysis, Phase 1 and Phase 2 FAS populations will be combined, and table summaries will be provided by treatment group and dose level; for disposition, baseline and demographic characteristics, prior and concomitant medication, medical history, and efficacy analysis, table summaries will be provided by treatment group and dose level for Phase 1 and by treatment group and expansion cohort (tumor type) for Phase 2.
- Section 6.5 was added to include the description for the calculation of study drug compliance. Planned tables for the summary of drug compliance were added to Appendix A.
- [redacted]

- Section 8.2.4 was updated to remove AE summary tables that were not important.
- A summary table and a listing were planned for orotic acid, BUN/urea, and ammonia for potential urea cycle inhibition and added to Appendix A.

In addition, other minor, administrative changes have been incorporated throughout the SAP and are noted in the redline version of the amendment.

11. REFERENCES

[redacted]

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

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Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med 2008;27:3145-3154.

Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. J R Stat Soc Ser C Appl Stat 2015;64:507-523.

APPENDIX A. PLANNED TABLES AND FIGURES

This appendix provides a list of the planned tables and figures for the clinical study report. Standard tables will follow the conventions in the Standard Safety Tables version.

The lists of tables, figures, and listings and the shells are to be used as guidelines. Modifications to the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard	In-Text
1.1 Disposition				
1.1.1.1	Summary of Participants Screened and Screen Failures	All Enrolled	X	X
1.1.1.2	Analysis Populations	Phase 1 FAS	X	X
1.1.1.3	Analysis Populations	Phase 2 FAS	X	X
1.1.2.1	Summary of Participant Disposition	Phase 1 FAS	X	X
1.1.2.2	Summary of Participant Disposition	Phase 2 FAS	X	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	FAS	X	
1.2 Demography				
1.2.1	Summary of Demographics	Phase 1 FAS	X	X
1.2.2	Summary of Demographics	Phase 2 FAS	X	X
1.3 Baseline Characteristics				
1.3.1.1	Summary of Baseline Disease Characteristics and Disease History – Solid Tumor Types	Phase 1 FAS	X	
1.3.1.2	Summary of Baseline Disease Characteristics and Disease History – Solid Tumor Types	Phase 2 FAS	X	
1.3.3.2	Summary of Baseline Disease Characteristics and Disease History – Colorectal Cancer	Phase 2 FAS	X	
1.3.4.2	Summary of Baseline Disease Characteristics and Disease History – Endometrial Cancer	Phase 2 FAS	X	
1.3.5.2	Summary of Baseline Disease Characteristics and Disease History – Gastric Cancer	Phase 2 FAS	X	
1.3.9.2	Summary of Baseline Disease Characteristics and Disease History – Ovarian Cancer	Phase 2 FAS	X	
1.3.11.2	Summary of Baseline Disease Characteristics and Disease History – Cholangiocarcinoma	Phase 2 FAS	X	
1.4 Prior Medication and Concomitant Medication				
1.4.1.1	Summary of Prior Systemic Therapy	Phase 1 FAS	X	
1.4.1.2	Summary of Prior Systemic Therapy	Phase 2 FAS	X	
1.4.2.1	Summary of Prior Medications	Phase 1 FAS	X	
1.4.2.2	Summary of Prior Medications	Phase 2 FAS	X	
1.4.3.1	Summary of Prior Radiation	Phase 1 FAS	X	
1.4.3.2	Summary of Prior Radiation	Phase 2 FAS	X	
1.4.4.1	Summary of Prior Surgery	Phase 1 FAS	X	
1.4.4.2	Summary of Prior Surgery	Phase 2 FAS	X	
1.4.5.1	Summary of Concomitant Medications	Phase 1 FAS	X	
1.4.5.2	Summary of Concomitant Medications	Phase 2 FAS	X	

Table No.	Title	Population	Standard	In-Text
1.5 Others				
1.5.1	Summary of General Medical History	Phase 1 FAS	X	
1.5.2	Summary of General Medical History	Phase 2 FAS	X	
1.5.3	Summary of Protocol Deviations	FAS		X
2.1 Efficacy				
2.1.1	Summary of Confirmed Best Overall Response, Objective Response Rate, Duration of Response, and Disease Control Rate Under RECIST v1.1 – by Treatment Group and Dose Level	Phase 1 Response Evaluable Population		X
2.1.2	Summary of Confirmed Best Overall Response, Objective Response Rate, Duration of Response, and Disease Control Rate Under RECIST v1.1 – by Treatment Group and Tumor Type	Phase 2 Response Evaluable Population		X
2.2.1	Summary of Progression-Free Survival Under RECIST v1.1 – by Treatment Group and Dose Level	Phase 1 FAS		X
2.2.2	Summary of Progression-Free Survival Under RECIST v1.1 – by Treatment Group and Tumor Type	Phase 2 FAS		X
[redacted]				
3.1 Dose Exposure				
3.1.1.1	Summary of INCB001158 Drug Exposure – by Treatment Group and Dose Level	FAS	X	X
3.1.1.2	Summary of INCB001158 Drug Compliance – by Treatment Group and Dose Level	FAS	X	X
3.1.2.1	Summary of Oxaliplatin Drug Exposure – by Treatment Group and Dose Level	mFOLFOX6 FAS	X	X
3.1.2.2	Summary of Leucovorin Drug Exposure – by Treatment Group and Dose Level	mFOLFOX6 FAS	X	X
3.1.2.3	Summary of 5-Fluorouracil Drug Exposure – by Treatment Group and Dose Level	mFOLFOX6 FAS	X	X
3.1.3.1	Summary of Gemcitabine Drug Exposure – by Treatment Group and Dose Level	Gemcitabine/ Cisplatin FAS	X	X
3.1.3.2	Summary of Cisplatin Drug Exposure – by Treatment Group and Dose Level	Gemcitabine/ Cisplatin FAS	X	X
3.1.4.1	Summary of Paclitaxel Drug Exposure – by Treatment Group and Dose Level	Paclitaxel FAS	X	X
3.2 Adverse Events				
3.2.1	Overall Summary of Treatment-Emergent Adverse Events – by Treatment Group and Dose Level	FAS	X	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term – by Treatment Group and Dose Level	FAS	X	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.4	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.5	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X

Table No.	Title	Population	Standard	In-Text
3.2.6	Summary of INCB001158 Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.7	Summary of mFOLFOX6 Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Dose Level	mFOLFOX6 FAS	X	X
3.2.8	Summary of Gemcitabine/Cisplatin Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Dose Level	Gemcitabine/ Cisplatin FAS	X	X
3.2.9	Summary of Paclitaxel Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Dose Level	Paclitaxel FAS	X	X
3.2.10	Summary of Grade 3 or Higher INCB001158 Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.11	Summary of Treatment-Emergent Adverse Events Leading to INCB001158 Dose Reduction by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.12	Summary of Treatment-Emergent Adverse Events Leading to INCB001158 Dose Interruption by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.13	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB001158 by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.14	Summary of fatal Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term – by Treatment Group and Dose Level	FAS	X	X
3.2.15	Summary of Immune-Related Treatment-Emergent Adverse Events (Investigator-Identified) by MedDRA Preferred Term in Decreasing Order of Frequency – by Treatment Group and Dose Level	FAS	X	X
3.2.16	Overall Summary of Immune-Related Treatment-Emergent Adverse Events (Investigator-Identified) – by Treatment Group and Dose Level	FAS	X	X
3.3 Laboratory				
3.3.1	Summary of Laboratory Values – Hematology	FAS	X	
3.3.2	Summary of Treatment-Emergent Worsening of Laboratory Abnormalities – Hematology	FAS	X	
3.3.3	Summary of Laboratory Values – Chemistry	FAS	X	
3.3.4	Summary of Treatment-Emergent Worsening of Laboratory Abnormalities – Chemistry	FAS	X	
3.3.5	Summary of Clinical Laboratory Values Indicative of Potential Urea Cycle Inhibition	FAS		
3.4 Vital Signs				
3.4.1	Summary of Systolic Blood Pressure (mmHg)	FAS	X	
3.4.2	Summary of Diastolic Blood Pressure (mmHg)	FAS	X	
3.5 ECGs				
3.5.8	Summary of Outliers of QT, QTc, QTcB, and QTcF Interval Values (ms) from 12-Lead ECG by Visit	FAS	X	X

Figures

Figure No.	Title	Population
2.1.1	Kaplan-Meier Estimates of Progression-Free Survival	Phase 1 FAS
2.1.2	Kaplan-Meier Estimates of Progression-Free Survival	Phase 2 FAS
[redacted]		
2.3.1	Swim Plot of Duration of Response (confirmed) – by Treatment Group and Dose	Phase 1 FAS
2.3.2	Swim Plot of Duration of Response (confirmed) – by Treatment Group and Tumor Type	Phase 2 FAS
2.4.1	Waterfall Plot of Percent Change from Baseline in Sum of Target Lesions – by Treatment Group and Dose Level	Phase 1 FAS
2.4.2	Waterfall Plot of Percent Change from Baseline in Sum of Target Lesions – by Treatment Group and Tumor Type	Phase 2 FAS
2.5.1	Spider Plot of Percent Change from Baseline in Sum of Target Lesions – by Treatment Group and Dose Level	Phase 1 FAS
2.5.2	Spider Plot of Percent Change from Baseline in Sum of Target Lesions – by Treatment Group and Tumor Type	Phase 2 FAS
6.3.1	Box-and-Whisker Plot of Maximum Orotic Acid Elevation	FAS

Listings

Listing No.	**Title**
2.1.2	Participant Enrollment and Disposition Status
2.1.3	Participant Inclusion and Exclusion Criteria Violations
2.2.1	Protocol Deviations and Violations
2.3.1	Analysis Populations
2.4.1	Demographics
2.4.2.1	Baseline Disease Characteristics – Solid Tumor Types
2.4.2.2	Baseline Disease Characteristics –Breast Cancer
2.4.2.3	Baseline Disease Characteristics – Colorectal Cancer
2.4.2.4	Baseline Disease Characteristics – Endometrial Cancer
2.4.2.5	Baseline Disease Characteristics – Gastric Cancer
2.4.2.6	Baseline Disease Characteristics – Non–Small Cell Lung Cancer
2.4.2.7	Baseline Disease Characteristics – Ovarian Cancer
2.4.2.8	Baseline Disease Characteristics – Pancreatic Cancer
2.4.2.9	Baseline Disease Characteristics – Cholangiocarcinoma
2.4.4	Prior Radiation Treatment
2.4.5	Prior Systemic Therapy
2.4.6	Prior Surgery or Surgical Procedure
2.4.7	Medical History
2.4.8	Prior and Concomitant Medication
2.4.9	Post-Treatment Anticancer Therapy
2.5.1.1	Study Drug Administration for INCB001158
2.5.1.2	Study Drug Compliance for INCB001158
2.5.2	Study Drug Administration for mFOLFOX6
2.5.3	Study Drug Administration for Gemcitabine/Cisplatin
2.5.4	Study Drug Administration for Paclitaxel
[redacted]	

2.6.3.1.1	Overall Response Assessment Under RECIST v1.1 – Phase 1
2.6.3.1.2	Overall Response Assessment Under RECIST v1.1 – Phase 2
[redacted]	
2.6.4.1	Response Assessment: Target Lesions – Phase 1
2.6.4.2	Response Assessment: Target Lesions – Phase 2
2.6.5.1	Response Assessment: Non-Target Lesions – Phase 1
2.6.5.2	Response Assessment: Non-Target Lesions – Phase 2
2.6.6.1	Response Assessment: New Lesions– Phase 1
2.6.6.2	Response Assessment: New Lesions – Phase 2
2.6.7.1	ECOG Status – Phase 1
2.6.7.2	ECOG Status – Phase 2
2.6.8.1	Confirmed Best Overall Response, Objective Response Rate, Duration of Response Under RECIST v1.1
2.6.8.2	Confirmed Best Overall Response, Objective Response Rate, Duration of Response Under RECIST v1.1
2.7.1	Adverse Events
2.7.2	Dose-Limiting Toxicities
2.7.3	Serious Adverse Events
2.7.4	Fatal Adverse Events
2.7.5	Adverse Events Leading to Discontinuation of INCB001158
2.7.6	Investigator-Identified Immune-Related Adverse Events
2.8.1.1	Clinical Laboratory Values – Hematology
2.8.1.2	Clinical Laboratory Values – Chemistry
2.8.1.3	Clinical Laboratory Values – Orotic Acid, BUN/Urea, and Ammonia for Potential Urea Cycle Inhibition
2.8.1.4	Abnormal Clinical Laboratory Values – Hematology
2.8.1.5	Abnormal Clinical Laboratory Values – Chemistry
2.8.1.6	PK Blood Sampling Times
2.8.2.1	Vital Signs
2.8.2.2	Abnormal Vital Sign Values
2.8.3.1	12-Lead Local ECG Values
2.8.3.2	Abnormal 12-Lead Local ECG Values